

WHAT IS CLAIMED:

1. An isolated nucleic acid molecule, comprising a sequence of nucleotides that encodes a polypeptide as set forth in SEQ ID No. 2, except that the Ile residue at position 646 of SEQ ID NO: 2 is replaced
5 with Val, Leu or Phe.
2. An isolated nucleic acid molecule of claim 1, wherein the residue at position 646 of SEQ ID NO: 2 is Val.
- Subj 3* 3. An isolated nucleic acid molecule of claim 1, comprising the sequence of nucleotides set forth as position 138 to position 2126 of SEQ
10 ID NO: 1, except that the nucleotide at position 2073 of SEQ ID NO: 1 is replaced with a nucleotide selected from the group consisting of G, T and
C.
4. The nucleic acid molecule of claim 3, wherein the nucleotide at position 2073 of SEQ ID NO: 1 is G.
- 15 5. The isolated nucleic acid molecule of claim 2, comprising nucleotides from position 138 to position 2126 of SEQ ID NO: 3.
6. An isolated nucleic acid molecule, comprising at least 14 or 16 contiguous nucleotides of SEQ. ID. NO: 3; wherein the contiguous nucleotides include a sequence of 5 contiguous nucleotides as set forth
20 from position 2069 to position 2077 of SEQ. ID. NO: 3.
7. The isolated nucleic acid molecule of claim 6, comprising at least 30 contiguous nucleotides of SEQ. ID. NO: 3.
8. The isolated nucleic acid molecule of claim 6, comprising at least 50 contiguous nucleotides of SEQ. ID. NO: 3.
- Subj 4* 25 9. A portion of the polypeptide of encoded by the nucleic acid molecule of claim 1, comprising at least 5 or 6 amino acid residues including the replaced residue at position 646 of SEQ ID NO: 2.
10. The polypeptide of claim 9, wherein the residue at position 646 of SEQ ID NO: 2 is Val.
- 30 11. A primer, probe or antisense nucleic acid molecule, comprising a sequence of nucleotides that specifically hybridizes adjacent

to or at a polymorphic region spanning a position corresponding to position 2073 of SEQ ID No. 1 or 3 of an AKAP10 allele or the complement thereof.

12. The primer, probe or antisense nucleic acid molecule of claim 5 11, wherein the hybridization refers to hybridization under moderate or high conditions.

13. A primer of claim 11, that specifically hybridizes at a position immediately adjacent to a position corresponding to position 2073 of SEQ ID NO: 1 or 3 of an AKAP10 allele.

10 14. A primer of claim 11, that is extended by a nucleotide that specifically base pairs with the nucleotide at a position corresponding to position 2073 of SEQ ID NO: 3 of an AKAP10 allele.

15. The primer, probe or antisense nucleic acid molecule of claim 11, that is single-stranded and contains at least 14 or 16 15 contiguous nucleotides of the AKAP10 allele or complement thereof, wherein the sequence of nucleotides includes at least 5 contiguous nucleotides from position 2069 to position 2077 of SEQ. ID. NO: 3.

16. The primer, probe or antisense nucleic acid molecule of claim 15, wherein nucleotide at position 2073 of SEQ ID NO: 1 is replaced with 20 a nucleotide selected from the group consisting of G, C or T.

17. The isolated nucleic acid molecule of claim 11, comprising at least 20 contiguous nucleotides of SEQ. ID. NO: 3, or the complement thereof.

18. The isolated nucleic acid of claim 11, comprising at least 30 25 contiguous nucleotides of SEQ. ID. NO: 3, or the complement thereof.

19. A nucleic acid vector, comprising the nucleic acid molecule of claim 1.

20. A cell containing the nucleic acid vector of claim 19.

21. A method for detecting the presence or absence of an allelic 30 variant of a human AKAP10 gene, comprising determining the identity of the nucleotide at a position corresponding to position 2073 of the coding

sequence of a human AKAP10 gene or the complement thereof, wherein a variant has a nucleotide other than A at a position corresponding to position 2073.

22. The method of claim 21, wherein determining the identity
5 comprises:

- (a) hybridizing a target nucleic acid comprising a human AKAP10-encoding nucleic acid or fragment thereof or a complement of a human AKAP10-encoding nucleic acid or fragment thereof with a nucleic acid primer that hybridizes adjacent to a position corresponding to
10 position 2073 of the coding sequence of the human AKAP10 gene or complement thereof;
- (b) extending the nucleic acid primer using the target nucleic acid as a template; and
- (c) determining the mass of the extended primer to identify the
15 nucleotide present at a position corresponding to position 2073 or the complement thereof, thereby determining the presence or absence of an allelic variant.

23. The method of claim 22, wherein the mass is determined by mass spectrometry.

20 24. The method of claim 22, wherein the primer is extended in the presence of at least one dideoxynucleotide,

25 25. The method of claim 24, wherein the at least one dideoxynucleotide is ddT.

26. The method of claim 24, wherein the primer is extended in
25 the presence at least two dideoxynucleotides and the at least two dideoxynucleotides are ddT and ddC.

27. The method of claim 26, wherein the mass is determined by mass spectrometry.

30 28. The method of claim 24, wherein the at least one dideoxynucleotide is ddA.

29. The method of claim 24, wherein the primer is extended in the presence at least two dideoxynucleotides and the at least two dideoxynucleotides are ddA and ddG.

30. The method of claim 29, wherein the mass is determined by 5 mass spectrometry.

31. The method of claim 22, wherein hybridization is effected under conditions of high stringency.

32. The method of claim 21, wherein determining the identity comprises:

10 (a) hybridizing a target nucleic acid comprising a human AKAP10-encoding nucleic acid, complement thereof or fragment thereof with a single-stranded nucleic acid probe at a position corresponding to position 2073 of the coding sequence of the human AKAP10 gene or complement thereof; and

15 (b) detecting hybridized probe to identify the nucleotide present at a position corresponding to position 2073 or the complement thereof, thereby determining the presence or absence of an allelic variant.

33. The method of claim 32, wherein hybridization is effected under conditions of high stringency.

20 34. The method of claim 32, wherein the nucleotide of the probe that hybridizes with the nucleotide at a position corresponding to position 2073 is complementary to a G, T, or C nucleotide.

35. The method of claim 32, wherein the nucleotide of the probe that hybridizes with the nucleotide at the complement of a position 25 corresponding to position 2073 is complementary to a G, A, or C nucleotide.

36. The method of claim 34, wherein the nucleotide detected at the position corresponding to position 2073 is a G.

37. The method of claim 35, wherein the nucleotide detected at 30 the complement of the position corresponding to position 2073 is a C.

38. A method for indicating susceptibility to morbidity, increased or early mortality, or morbidity and increased or early mortality of a subject, comprising:

detecting the presence or absence of at least one allelic variant of a
5 polymorphic region of an AKAP10 gene that is associated with susceptibility to morbidity, increased or early mortality, or morbidity and increased or early mortality, wherein:

the predominant allele comprises an "A" at a position corresponding to position 2073 of SEQ ID NO: 1; and

10 the presence of the allelic variant is indicative of increased susceptibility to morbidity, increased or early mortality, or morbidity and increased or early mortality compared to the susceptibility of a subject who does not comprise the allelic variant.

39. The method of claim 38, wherein a polymorphic region of the AKAP10 gene comprises a nucleotide other than an A at a position corresponding to position 2073 of the coding sequence of the AKAP10 gene or other than an T of the complement of the coding sequence of the AKAP10 gene.

40. The method of claim 38, wherein the detecting step is
20 effected by a method selected from the group consisting of allele specific hybridization, primer specific extension, oligonucleotide ligation assay, restriction enzyme site analysis and single-stranded conformation polymorphism analysis.

41. The method of claim 38, wherein the detecting step
25 comprises mass spectrometry.

42. The method of claim 38, wherein detection is effected by detecting a signal moiety selected from the group consisting of radioisotopes, enzymes, antigens, antibodies, spectrophotometric reagents, chemiluminescent reagents, fluorescent reagents and other light
30 producing reagents.

43. The method of claim 39, further comprising:

detecting an allelic variant at another polymorphic region of an AKAP10 gene selected from the group consisting of a position corresponding to position 83587 of SEQ ID NO: 13, a position corresponding to position 129,600 of SEQ ID NO: 14 and a position 5 corresponding to position 156,277 of SEQ ID NO: 18.

44. A cell, comprising heterologous nucleic acid that encodes a human AKAP10 variant protein or portion that exhibits a biological activity of the full length variant protein, wherein the AKAP10 variant protein or portion thereof comprises valine at a position corresponding to 10 the position of amino acid residue 646 of SEQ ID NO: 2.

45. The cell of claim 44, wherein heterologous nucleic acid encodes the sequence of amino acids set forth in SEQ. ID. NO: 4.

46. The cell of claim 44, wherein the nucleic acid comprises the sequence of nucleotides set forth from position 138 to position 2126 of 15 SEQ. ID. NO: 3.

47. A kit for indicating whether a human subject has an increased susceptibility to morbidity or a predisposition for premature or increased or early mortality, comprising:

20 a first primer or probe of claim 11; and
a second primer or probe that specifically hybridizes adjacent to or at a polymorphic region spanning a position corresponding to positions selected from the group consisting of position 83587 of SEQ ID NO 13 or 17, position 129600 of SEQ ID NO 14 or 17, and position 156,277 of SEQ ID NO 18 or 17 of an AKAP10 allele or the complement thereof.

25 48. The kit of claim 47, further comprising instructions for use.

49. The kit of claim 47, further comprising at least one dideoxynucleotide.

50. The kit of claim 49, wherein the dideoxynucleotide is selected from the group consisting of ddA, ddC and ddG.

30 51. A method of producing a protein by growing the cell of claim 20 under conditions whereby the protein is expressed; and

isolating the protein.

52. The method of claim 51, wherein the cell is a mammalian cell, yeast cell, insect cell or bacterial cell.

53. The method of claim 51, wherein the cell is a human cell.

54. A protein produced by the method of claim 52.

55. A transgenic animal, comprising heterologous nucleic acid encoding a human AKAP10 variant protein or portion thereof which retains a biological activity exhibited by the full length variant protein, wherein the AKAP10 protein or portion thereof comprises valine at a 10 position corresponding to amino acid residue position 646 of SEQ ID NO: 2, wherein:

the transgenic nucleotide acid is expressed; and,

as a result of the expression, the transgenic animal has an alteration in cellular signal transduction.

15 56. The transgenic animal of claim 55, which is a mouse.

57. A method for identifying a molecule that modulates the biological activity of an AKAP10 protein, comprising:

20 (a) combining the candidate molecule with a cell comprising a nucleotide sequence encoding an AKAP10 protein which comprises an amino acid at a position corresponding to the position of residue 646 of SEQ ID NO: 2 which is not Ile or portion thereof that retains a biological activity exhibited by a full length variant protein, operably linked to a promoter such that the nucleotide sequence is expressed as an AKAP protein or portion thereof in the cell; and

25 (b) determining the affect of the molecule upon a biological activity of the AKAP10 protein or portion thereof.

58. The method of claim 57, wherein the biological activity of the AKAP protein or portion thereof is determined by examining signal transduction in the cell.

30 59. The method of claim 57, wherein the biological activity is the binding of AKAP10 protein or portion thereof to protein kinase A.

60. The method of claim 57, wherein the biological activity of the AKAP protein or portion thereof is determined by examining protein phosphorylation in the cell.

61. A method for indicating an alteration in signal transduction in
5 a subject, comprising:

detecting the presence or absence of an allelic variant of an AKAP10 gene having a nucleotide other than A at a position corresponding to position 2073 of SEQ ID NO: 1, wherein the presence of a nucleotide other than A is indicative of an alteration in signal
10 transduction.

62. The method of claim 61, wherein the allelic variant has a G at a position corresponding to position 2073 of SEQ ID NO: 1.

63. The method of claim 61, further comprising detecting the presence or absence of an allelic variant at another polymorphic position
15 of the AKAP10 gene selected from the group consisting of a position corresponding to position 83587 of SEQ ID NO: 13, position 129,600 of SEQ ID NO: 14 and position 156,277 of SEQ ID NO: 18.

64. The method of claim 61, wherein the alteration in signal transduction is related to a disorder selected from the group consisting of
20 cardiovascular disorders, cardiac disorders, proliferative disorders, neurological disorders, neurodegenerative disorders, obesity, diabetes and peripheral retinopathies.

65. The method of claim 64, wherein the disorders are selected from the group consisting of Alzheimer's disease, altered left ventricular
25 function, cardiomyopathies, bipolar disorder and retinitis pigmentosa.

66. The method of claim 61, wherein the detecting step is effected by a method selected from the group consisting of allele specific hybridization, primer specific extension, oligonucleotide ligation assay, restriction enzyme site analysis and single-stranded conformation
30 polymorphism analysis.

67. The method of claim 61, wherein the detecting step comprises mass spectrometry.

68. The method of claim 61, wherein the detecting step is effected a signal moiety selected from the group consisting of:

5 radioisotopes, enzymes, antigens, antibodies, spectrophotometric reagents, chemiluminescent reagents, fluorescent reagents and other light producing reagents.

69. A solid support comprising a nucleic acid comprising a polymorphic region of an AKAP10 gene, wherein the polymorphic region 10 comprises a nucleotide at a position corresponding to position 2073 of SEQ ID NO: 1 that is other than an A or other than T on the complementary strand.

70. The solid support of claim 69 which is a microarray.

71. The microarray of claim 70, further comprising a nucleic acid molecule that comprising the sequence of a polymorphic region of an AKAP10 gene corresponding to a position selected from the group consisting of position 83587 of SEQ ID NO: 13, position 129,600 of SEQ ID NO: 14 and position 156,277 of SEQ ID NO: 18.

72. An anti-AKAP10 ribozyme comprising a sequence 20 complementary to a polymorphic region of an AKAP10 gene.

73. The ribozyme of claim 72, in which the polymorphic regions are selected from the group consisting of a position corresponding to position 2037 of SEQ ID NO: 3, position 83587 of SEQ ID NO: 13, position 129,600 of SEQ ID NO: 14 and position 156,277 of SEQ ID NO: 25.

74. The ribozyme of claim 72, comprising SEQ ID NO: 25.

75. A primer consisting essentially of nucleotide sequences selected from the group consisting of SEQ ID NO: 8, SEQ ID NO: 15, SEQ ID NO: 19 and SEQ ID NO: 20.